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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/826,463	04/05/2001	Nobuto Yamamoto	Y1004/20017	2419

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EXAMINER	
ROMEO, DAVID S	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 05/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/826,463	YAMAMOTO, NOBUTO	
	Examiner	Art Unit	
	David S. Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22 and 24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *0206*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 02/17/2006 has been entered.

Claims 22 and 24 are pending and being examined.

Maintained Formal Matters, Objections, and/or Rejections:

Claim Rejections - 35 USC § 112

Claim 24 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant argues that he was able to determine the smallest domain containing an essential peptide for macrophage activation of a Gc protein using chemically and proteolytically fragmented Gc, as disclosed in the specification at page 10, lines 5-7. Applicant argues that the Haddad reference (Biochemistry. 1992 Aug 11;31(31):7174-81) teaches that it was known in the art to sequence peptides, and since this reference has been incorporated by reference the limitation in claim 24 is not new matter. Applicant's arguments have been fully considered but they are not persuasive.

The relevant portion of the specification is reproduced below:

> Domain I interacts with vitamin D while domain III interacts with actin (Haddad et al., Biochem., 31:7174, 1992). Chemically and proteolytically fragmented Gc enabled me to indicate that the smallest domain, domain III, contains an essential peptide for macrophage activation. Page 10, full paragraph 1.

This portion of the specification only refers to Haddad in regard to functional domains of the Gc protein. Furthermore, this portion only refers to chemically and proteolytically fragmented Gc.

The following portions from the Haddad reference seem most relevant for construing peptide sequencing:

> Pure hDBP was isolated as previously described (Haddad et al, 1984) or purchased (Calbiochem). Paragraph bridging pages 7174-7175.

> For peptides correlating with radioactivity in paired gel lanes, their stained membrane bands were isolated with a razor blade and were analyzed for amino-terminal sequence in an Applied Biosystems 473A protein sequencer. The results obtained were compared with the known sequence of hDBP (Cooke & David, 1985). Sequences for peptide fragments were then used to predict the likely enzyme cleavage site at the carboxy terminus of the identified peptide (Cooke & David, 1985). Page 7175, right column, full paragraph 1.

> Discrete bands were cut from the dried membrane and stored in dry vials until amino acid sequence analyses were performed. Page 7176, left column, first sentence.

> When a 50-kDa peptide from a trypsin digest was eluted from the native gel slice for size estimation by reducing SDS-PAGE, it was found also to exhibit specific binding of 25-OHD3. Therefore, the blotted peptide was analyzed for amino acid sequence at its amino terminus. Page 7176, left column, full paragraph 1.

> Amino acid sequencing from the amino termini of the fragments revealed two peptides cleaved at Lys-35 and one at Arg-5. Page 7177, left column, full paragraph 1.

> Following transfer of Pro-Blott membranes from 20-cm, 15% polyacrylamide gels run under denaturing and reducing conditions, both peptides were sequenced (Table I, section B). Page 7177, left column, last full paragraph.

Haddad also discloses *in vitro* transcription and translation of full-length and truncated rat DBP (page 7176, section bridging left and right columns). Table I (page 7178) shows the amino-terminal amino acid sequence of proteolytic fragments of hDBP. Haddad only discloses determining the amino-terminal sequence of proteolytic fragments of the Gc protein. Furthermore, the Haddad's Gc protein was isolated from its native source and not recombinantly, as evidenced by Haddad at Paragraph bridging pages 7174-7175 and the attached Gc protein product data sheet from Calbiochem.

This evidence cannot be fairly said to describe the concept of cloning a Gc1 isoform into a baculovirus vector and sequencing the cloned Gc1 peptide, thereby confirming that the cloned Gc1 protein is a cloned wild type Gc1 protein, because the evidence that Applicant relies upon only describes determining the amino-terminal sequence of various chemically and proteolytically fragments of a Gc protein isolated from its native source. The evidence relied upon does not describe cloning of a Gc protein and does not describe sequencing the full-length protein. Although it might be obvious to a skilled artisan to clone a Gc protein and confirm that the cloned Gc protein is wild-type by sequencing the cloned Gc protein, the written description does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed. It extends only to that which is disclosed. One shows that one "had possession" of the invention by describing the invention, with all its claimed limitations, not that which makes it obvious. Applicant's arguments are therefore not persuasive.

Claim Rejections - 35 USC § 103

Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yamamoto (U. S. Patent No. 5,177,002) in view of Cooke (J Clin Invest. 1985 Dec;76(6):2420-4), Quirk (Biotechnol Appl Biochem. 1989 Jun;11(3):273-87), Lichenstein (U. S. Patent No. 5,652,352), Murphy (U. S. Patent No. 5,516,657), and Luckow (Baculovirus Expression Systems and Biopesticides, 1995 Feb:51-90).

Applicant argues that Ailor (Curr Opin Biotechnol. 1999 Apr;10(2):142-5) and Ho (Biochem J. 2004 Sep 1;382(Pt 2):695-702) teach that there are specific disadvantages to using the baculovirus expression system, and therefore it would not have been obvious to a skilled artisan to use a baculovirus vector because there was not a reasonable expectation of success. Applicant's arguments have been fully considered but they are not persuasive. There would appear to be specific disadvantages to using any expression system. However, one advantage of the Baculovirus vectors over bacterial and yeast expression vectors includes the expression of recombinant proteins that are essentially authentic and are antigenically and/or biologically active. In addition, Baculoviruses are not pathogenic to vertebrates or plants and do not employ transformed cells or transforming elements as do the mammalian expression systems. Although mammalian expression systems result in the production of fully modified, functional protein, yields are often low. *E. coli* systems result in high yields of recombinant protein but the protein is not modified and may be difficult to purify in a nondenatured state. See Murphy, column 1, lines 40-52. In contrast to Ailor's teachings, Luckow teaches that recombinant proteins expressed in insects cells are in many cases soluble and antigenically, immunogenically, and functionally similar to their authentic counterparts (page 51, full paragraph 1). Generally,

proteins expressed in baculovirus infected cells are directed to the appropriate cellular compartments for processing and targeted to their natural locations in the nucleus, cytoplasm, organelles, plasma membrane, or extracellular space (page 78, left column, full paragraph 1). With few exceptions, insect cells are able to recognize and properly cleave signal peptides that direct a protein into the endoplasmic reticulum for further processing and subsequent targeting to the cellular membranes or secretion into the extracellular space (paragraph bridging pages 78–79). Expression of foreign genes by baculovirus vectors permits the production of proteins that cannot often be achieved with other expression systems (page 83, last full paragraph). In addition, Ho teaches that, since its introduction in 1983, the BEVS (baculovirus expression vector system) has become one of the most popular protein expression systems used in industry and molecular biology laboratories. BEVSs have several advantages over other recombinant protein expression systems, including high protein yields, ease of use and safety. See page 695, left column, full paragraph 1. These indications attest to the reasonable expectations of one of ordinary skill in the art. As noted in the last Office action, obviousness does not require absolute predictability, only a reasonable expectation of success. In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness does not outweigh the evidence of obviousness.

Claims 22 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamamoto (U. S. Patent No. 5,177,002) in view of Cooke (J Clin Invest. 1985 Dec;76(6):2420-4), Quirk (Biotechnol Appl Biochem. 1989 Jun;11(3):273-87), Lichenstein (U. S. Patent No. 5,652,352), Murphy (U. S. Patent No. 5,516,657), and Luckow (Baculovirus Expression Systems

and Biopesticides, 1995 Feb:51-90) as applied to claim 22 above, and further in view of Lu (Protein Expr Purif. 1993 Oct;4(5):465-72).

Applicant argues that Ailor (Curr Opin Biotechnol. 1999 Apr;10(2):142-5) and Ho (Biochem J. 2004 Sep 1;382(Pt 2):695-702) teach that there are specific disadvantages to using the baculovirus expression system, and therefore it would not have been obvious to a skilled artisan to use a baculovirus vector because there was not a reasonable expectation of success. Applicant's arguments have already been fully considered but they are not persuasive for the reasons discussed above.

Applicant argues that the Lu reference weighs against the finding of obviousness because of the inherent problems with recombinant protein production. Applicant argues that there is no motivation to combine the references and there was not a reasonable expectation of success. Applicant's arguments have been fully considered but they are not persuasive. The ability of recombinant expression systems to produce proteins at level higher than the protein's native source, and the fact that expression of foreign genes by baculovirus vectors permits the production of proteins that cannot often be achieved with other expression systems (Luckow, page 83, last full paragraph) outweighs the evidence of nonobviousness. Furthermore, one of ordinary skill in the art would be motivated to combine the references in order to ensure the quality of the final product. As discussed above, the references attest to the reasonable expectations of one of ordinary skill in the art.

Conclusion

No claims are allowable.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, BRENDA BRUMBACK, CAN BE REACHED ON (571) 272-0961.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE CENTRAL FAX NUMBER FOR OFFICIAL CORRESPONDENCE, WHICH IS (571) 273-8300.

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

David Romeo

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
APRIL 18, 2006